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Myocardial Scarring After Transmyocardial Laser Revascularization: A Potential Mechanism of Clinical Improvement?

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Background and Objective: **The morphological evolution of transmyocardial laser channels was analyzed in a pig model.**
Materials and Methods: **Five channels were created in the lateral wall of the left ventricle of 12 animals, using a Ho:YAG laser. In half of the animals, an additional infarction was induced in the same area. Animals were sacrificed at one-week intervals until week 5 and the critical regions of the left ventricular wall were subjected to microscopic computed morphometrical analysis.**
Results: **There was no clearly patent lumen at any stage. Cross-sectional area of the channels fell from 8.5 ± 1.2 mm^2 at day 0 to 2.1 ± 0.1 mm^2 at day 35. From day 7 onward, the channel area was gradually replaced by granulation tissue and the proportion of the channel occupied by granulation scar tissue increased from 37 ± 2% at day 7 to 100% at day 28. In the subgroup with concomitant infarction, granulation tissue of both channel and infarction became indistinguishable from day 14 onward.**
Conclusions: **These results suggest strongly that channel patency is not the mechanism of angina relief after transmyocardial laser revascularization with Ho:YAG laser. Lasers Surg. Med. 25:79–87, 1999.** **© 1999 Wiley-Liss, Inc.**

Key words: histology; myocardium

INTRODUCTION

Transmyocardial laser revascularization (TMLR) has emerged as an alternative treatment for patients with symptomatic coronary artery disease who are refractory to maximal medical therapy and unsuitable for coronary artery bypass graft or percutaneous transluminal angioplasty [1].

Mirhoseini et al. [2] were the first to propose using a laser to create transmyocardial channels with the aim to provide direct perfusion of the myocardium with ventricular blood. This technique has been demonstrated to improve functional class of angina pectoris [1,3,4]. However, clinical and experimental evidence of channel patency has been conflicting [5–22]. Other mechanisms such as neoangiogenesis elicited by laser injury [23] or fiber nerve destruction [24] have been suggested as potential mechanisms for clinical improvement. Most experimental studies tested transmyocardial laser channels in dog hearts, which have variable native collateral. In

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contrast, pig hearts have very little native collateral circulation, which eliminates the potentially confounding variable of collateral blood flow.

The purpose of this study was to analyze the sequential macroscopic and microscopic evolution of laser-induced channels associated or not with infarction, with special attention paid to channel patency and size of the lesions.

MATERIALS AND METHODS

Laser Variables

To create the laser channels, we used a holmium:yttrium-aluminium garnet (Ho:YAG) laser (CardioGenesis TMLR System, Santa Clara, CA), which emits a burst of three pulses of energy at the 2.1 μm wavelength, which is invisible radiation in the mid-infrared portion of the spectrum. The pulsewidth is 350 μs in duration. The output of the holmium:YAG laser is focused into a 365 μ core diameter low-OH quartz fiber with a cylindrical tip (1.75 mm diameter). A 633 nm Helium neon laser beam is used as an aiming beam. The pulse repetition rate is 16 Hz for a burst of three pulses and the energy per pulse is 2.0 J. The emission of pulses are synchronized with the R wave of the ECG monitoring in order to avoid arrhythmias.

Animal Preparation

The study was performed in 12 pigs weighing between 64 and 77 kg (mean, 71 ± 4.2 kg). The animals were premedicated with Ketaminol (10 mg/kg) and Atropine (2 mg) injected intramuscularly. Vascular access was established through a vein of the ear. After induction with sodium thiopental (5 mg/kg) through this venous line, the animals were intubated and anesthesia was maintained by intravenous administration of sodium thiopental as needed. Animals were ventilated with room air. Respiratory rate and stroke volume were adjusted to maintain arterial blood gases within the normal physiologic range. Three ECG leads were installed. A left lateral cervicotomy was performed to provide vascular access. An arterial line was inserted into the carotid artery and a Swan-Ganz catheter was inserted through the jugular vein into the pulmonary artery to measure pressures of the right sided heart chambers. A left lateral thoracotomy was performed through the fifth intercostal space. The pericardium was opened and reflected to form a cradle for suspending the heart. Thirty minutes were allowed for stabilization after the completion of surgery.

Experimental Protocol

The animals were randomized either to a TMLR group (six animals) or a TMLR and myocardial infarction (TMLR-MI) group (six animals). In the first group, five transmural channels were created at the mid-height of the left lateral wall, 1 cm apart. Epicardial opening of each channel was marked with a nonresorbable stitch, in order to locate them later for histology. A channel was considered transmural when blood spurted out of its epicardial opening. In the TMLR-MI group, the same procedure was performed, followed 30 minutes later by ligation of several marginal branches of the circumflex artery, in order to induce an acute myocardial infarction in the laser-treated area of the left ventricle. The drilling of the channels was performed first, in order to avoid using the laser on an acutely ischemic myocardium, which would have carried a too high risk of intractable ventricular arrhythmias. At the end of the operation, the thoracotomy was closed on a chest tube, which was removed after the weaning from the ventilator.

Sacrifice

In each group, one animal was sacrificed at days 0, 7, 14, 21, 28, and 35 after the initial operation. After an intravenous bolus injection of saturated potassium chloride, the heart was rapidly excised for fixation in 4% buffered formaldehyde for histology.

Histology and Morphometry

The endocardium was examined for all channel openings in order to assess their permeability. Channel area, with or without infarction, was excised and sliced perpendicular to the channel axis at the mid-level of the myocardial thickness. A tissue block from the middle-third of the ventricular wall was chosen, dehydrated, and embedded in paraffin. Serial sections were stained with hematoxylin and eosin, and with Masson's trichrome stain for microscopic analysis. The areas of interest were digitized by an image analysis system (Image Pro 3.0, Media Cybernetics, MD). The cross-sectional area of the channels were delineated with a cursor and converted from pixels to mm^2 through a calibration procedure by use of a reference system.

Data are expressed as mean ± 1 standard deviation.

RESULTS

Macroscopic Evaluation of the Laser Channels

In both groups, the hearts examined immediately after application of the laser showed patent endocardial channel openings. In the TMLR group these openings were occluded by a clot at day 7, and from day 14 onward they were completely replaced by a whitish scar. All the endocardial channel ends could be located. The same finding was present in the TMLR-MI group at day 7, where all the endocardial channel ends were within the infarction area. However from day 14 onward, the endocardial channel ends could not be identified anymore either inside or outside the infarct. Therefore we concluded that the scarring process of both channels and infarction became indistinguishable at this time point.

Microscopic Evaluation of the Laser Channels of the TMLR Group

In samples obtained immediately after application of the laser, the channels had generally an elliptic configuration (Fig. 1a). Similarly to previous studies [5,6] four concentric zones could be identified along the channel path (Fig. 1b). The central zone was filled with serous fluid containing red cells within a fibrin network, consistent with a fresh clot. This was surrounded by a zone of thermal necrosis containing partially vaporized tissue and coagulated protein. At the periphery, a transition zone was observed, showing a progressively changing pattern with an outer layer in which myocardial fibers exhibit irregular contraction bands.

At day 7 (Fig. 2), both occurred: the central zone filled with a clot, and the zone of thermal necrosis persisted. They were surrounded by a zone of granulation tissue with numerous capillaries and delicate collagen network. The cellular elements of this zone consisted mainly of fibrocytes, and in the near vicinity of the zone of thermal necrosis there were numerous inflammatory cells, as well as a few macrophages, some of which containing intracytoplasmic deposits of lipofuscin.

At day 14, the central area surrounded by occasional residual debris was smaller. The peripheral granulation tissue contained more collagen but fewer capillaries and cellular elements.

At day 21, the central clot area was only occasionally present. Generally the channels were completely replaced by a predominantly acellular scar tissue. At days 28 (Fig. 3) and 35, the findings were the same with a uniform scar tissue throughout the channel areas containing some thin walled blood vessels.

Microscopic Evaluation of the Laser Channels of the TMLR-MI Group

The findings were essentially the same as in the TMLR group, with the difference that from day 14 onward, the granulation tissue and the scarring processes of both channels and infarction became indistinguishable. Figure 4 shows the border of a channel within the infarction area at day 7, when both lesions are still distinguishable.

Morphometrical Analysis of the Channels

Table 1 show the sequential evolution of the laser channel area. The area fell from 8.5 ± 1.2 mm^2 at day 0 to 2.1 ± 0.1 mm^2 at day 35, representing a 75.3% reduction. The initial lesion was actually three to four times as large as the 2.4 mm^2 cross section of the probe, whereas the scar area, after 35 days, was of the same order of magnitude. When analyzing the proportions occupied by the dead tissue and the granulation scar tissue from day 7 onward, the progressive complete replacement of the channel by fibrous tissue becomes evident (Table 1).

DISCUSSION

This morphological analysis of channels created with the Ho:YAG laser in a pig model could not detect any evidence of channel patency at any time interval, in both ischemic and nonischemic settings. In the group with channels drilled in healthy myocardium, the channels were initially filled with amorphous proteinaceous material. Over the ensuing weeks they were progressively invaded by the ingrowth of fibroblasts and new vessels similar to the healing response found after myocardial infarction [25,26]. Mallory et al. [27] described the speed of healing of a myocardial infarction as dependent upon the size of the lesion, small infarcts being almost completely healed after five weeks and large infarcts completely healed after two months. The timing of the scarring process after TMLR is in accordance with this description, as the laser-treated areas are tiny in comparison with myocardial infarction and they undergo no further change after four weeks. In the group with concomitant infarction, the same sequence of events was observed, but from day 14 onward, granulation tissue resulting from both channel and infarction areas became

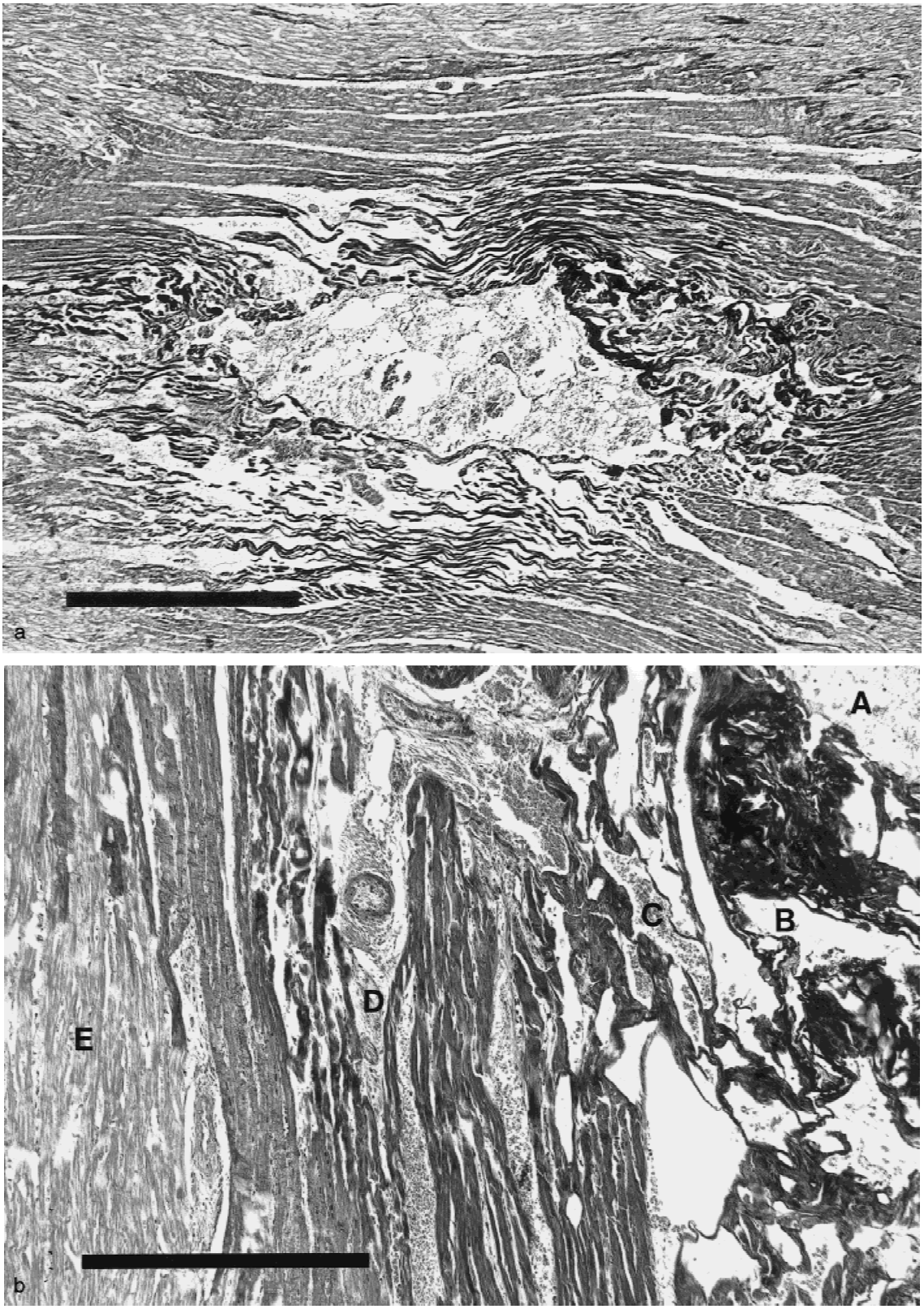

Fig. 1. Acute channel at day 0 (Trichrome Masson stain). (**a**) Overview of the channel (scale = 1 mm). (**b**) Higher magnification (scale = 0.5 mm). The four zones are shown: A = central zone filled with a fresh clot; B = zone of thermal necrosis; C = transition zone; D = peripheral zone with myocardial fibers exhibiting irregular contraction bands; E = normal myocardium.

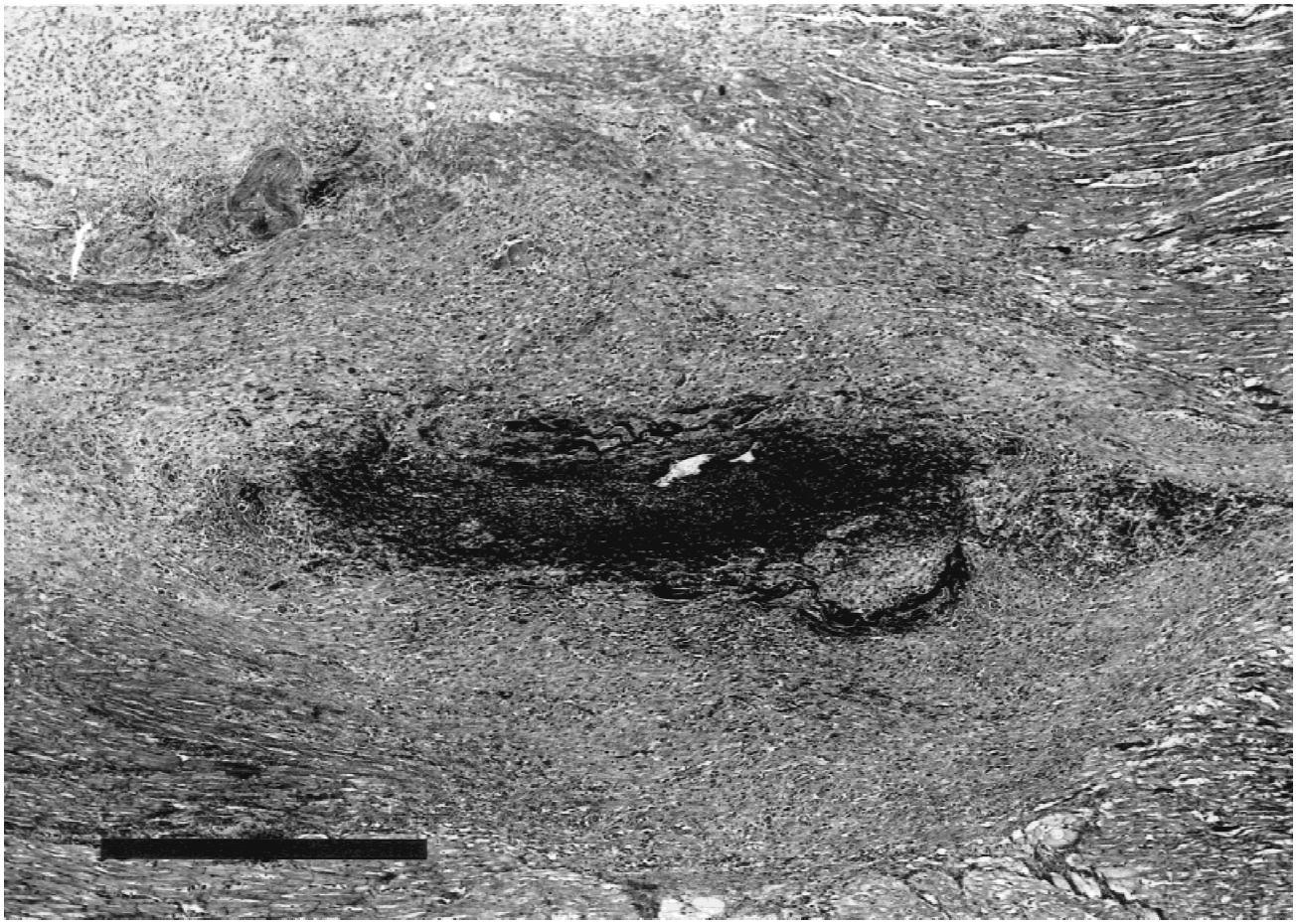

Fig. 2. Channel area at day 7. The central zone filled with a clot, and the zone of thermal necrosis are still present. Beyond them there is a new zone of granulation tissue rich in capillaries and collagen networks. (Trichrome Masson stain; scale = 1 mm).

indistinguishable. These findings support the absence of blood flow through the channels from the ventricular cavity in both situations. On macroscopic examination of the endocardial surface in both groups, all channel entry points were occluded as soon as day 7, providing definitive evidence for the absence of blood flow from the ventricular cavity, even in the early phase of channel healing.

Among the bulk of experimental work on TMLR, only two groups have formally addressed its histological analysis [5,6]. Hardy et al. [5] by using a CO_2 laser in a nonischemic canine model, found within the central zone of vaporization, a channel initially filled with serous fluid and replaced after 24 hours by a coagulum. These areas were surrounded by a narrow zone of carbonization and a broader zone of thermal fixation. From day 6 though 10, channels were partially to completely occluded by scarring tissue. At two weeks the channels were no longer "patent" at any level and by the fourth week they were reduced to retracted scars. The relative size of the irreversible laser damage diminished from 1.4 mm^2 at day 0 to 0.42 mm^2 at day 28. In the same animal, Fischer et al. [6] compared the histology of channels made with CO_2 laser and Ho:YAG laser. Both types of channels exhibited the same histological evolution as described by Hardy et al. [5]. The channels were initially occluded with a thrombus and surrounded by a zone of thermal necrosis and a zone of contraction band necrosis. These lesions were progressively replaced by neovascularized collagen at 2–3 weeks. The scarred channel entry point on the endocardial surface were not patent macroscopically in any of the chronic studies. The only difference between both types of channels lies in the size of the channel core and the area of thermally damaged tissue, which were larger with the Ho:YAG laser, as is predicted by the differing en-

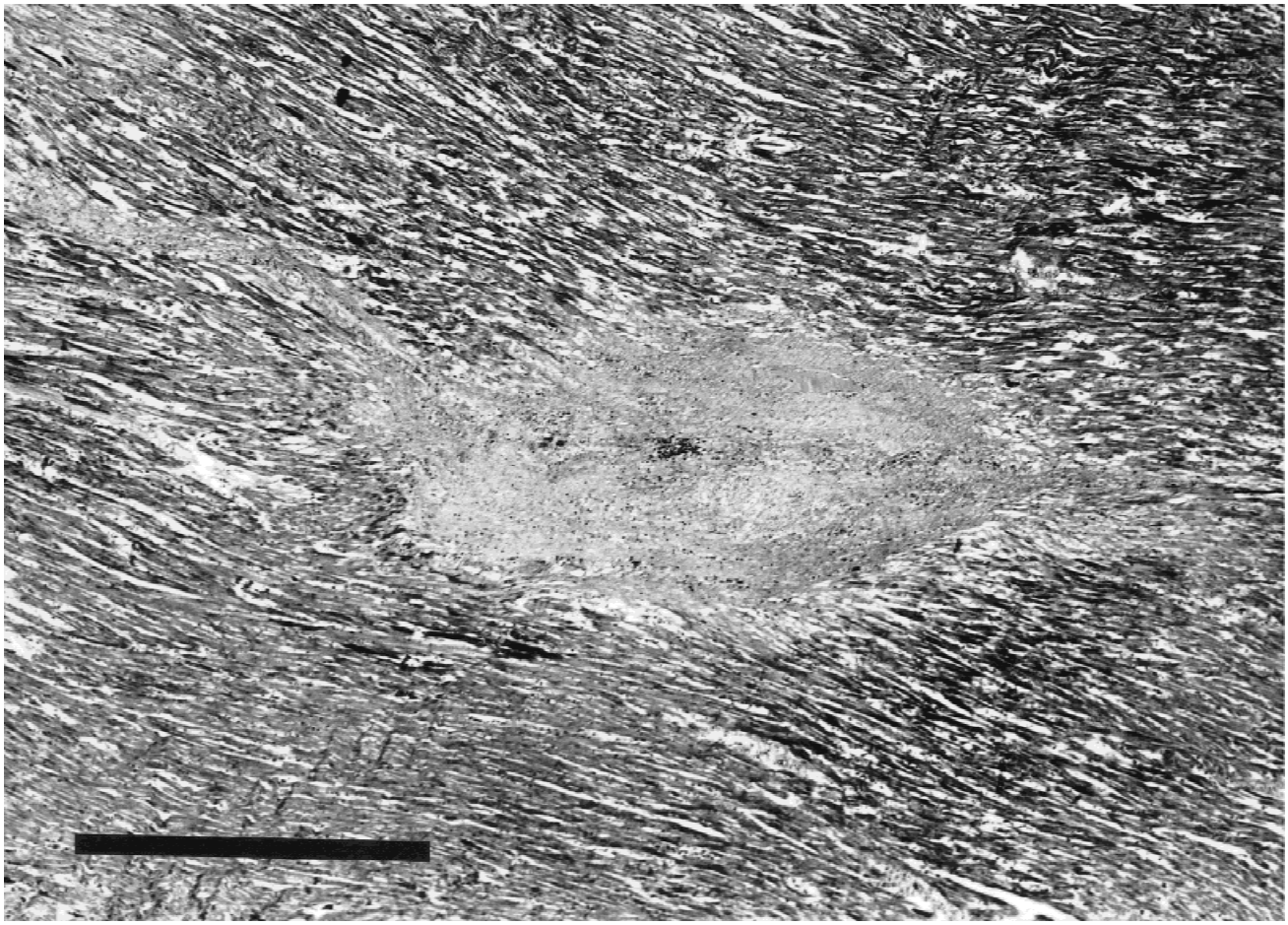

Fig. 3. Channel scar area at day 28. Uniform scar tissue throughout the channel area. (Trichrome Masson stain; scale = 1 mm).

ergy characteristics of these two laser beams [28]. Thus, our study performed in a model with no significant collateral circulation, exhibits findings similar to these studies performed on a canine model. Moreover, we provide a direct comparison between channels performed in healthy vs. ischemic myocardium. Khomoto, in a separate report [16], performed CO_2 laser channels after coronary ligation in the dog and found at two weeks that many channels were obscured by the massive healing response incited by the infarction.

Other experimental works reported isolated histological findings, which were interpreted as patent channels [7,8]. However, the size of these so called patent channels ranged between 10 and 75 μm in striking contrast to the original CO_2 laser channel diameters of 1 mm. Mack et al. [29] used an excimer laser and found too so called "channel derivative" whose lumen ranged from 10 to 100 μm. These dimensions are similar to the vascular structures within the scarred channel region observed in our animals. Therefore these structures may be rather interpreted as scarred channel remnants. Notably these studies did not describe the macroscopic aspect of the endocardial surface.

The initial size of the laser lesion is much larger than that of the laser probe (8.5 ± 1.2 mm^2 vs. 2.4 mm^2). This feature was also found by Lutter et al. [30] in the heart of a patient who died two hours after TMLR with a CO_2 laser. Thus in the acute setting, TMLR might be potentially deleterious on the left ventricular function and should be used cautiously in patients with reduced left ventricular contractile reserve.

As suggested by Jansen et al. [31] the elliptic morphology of the channels could be explained by the asymmetric distribution of thermal damage, which can be seen as a more extensive zone of thermally altered tissue coaxial with the direction of myofibrils (i.e., along the fibers) as compared with the zone of thermal damage perpendicular to

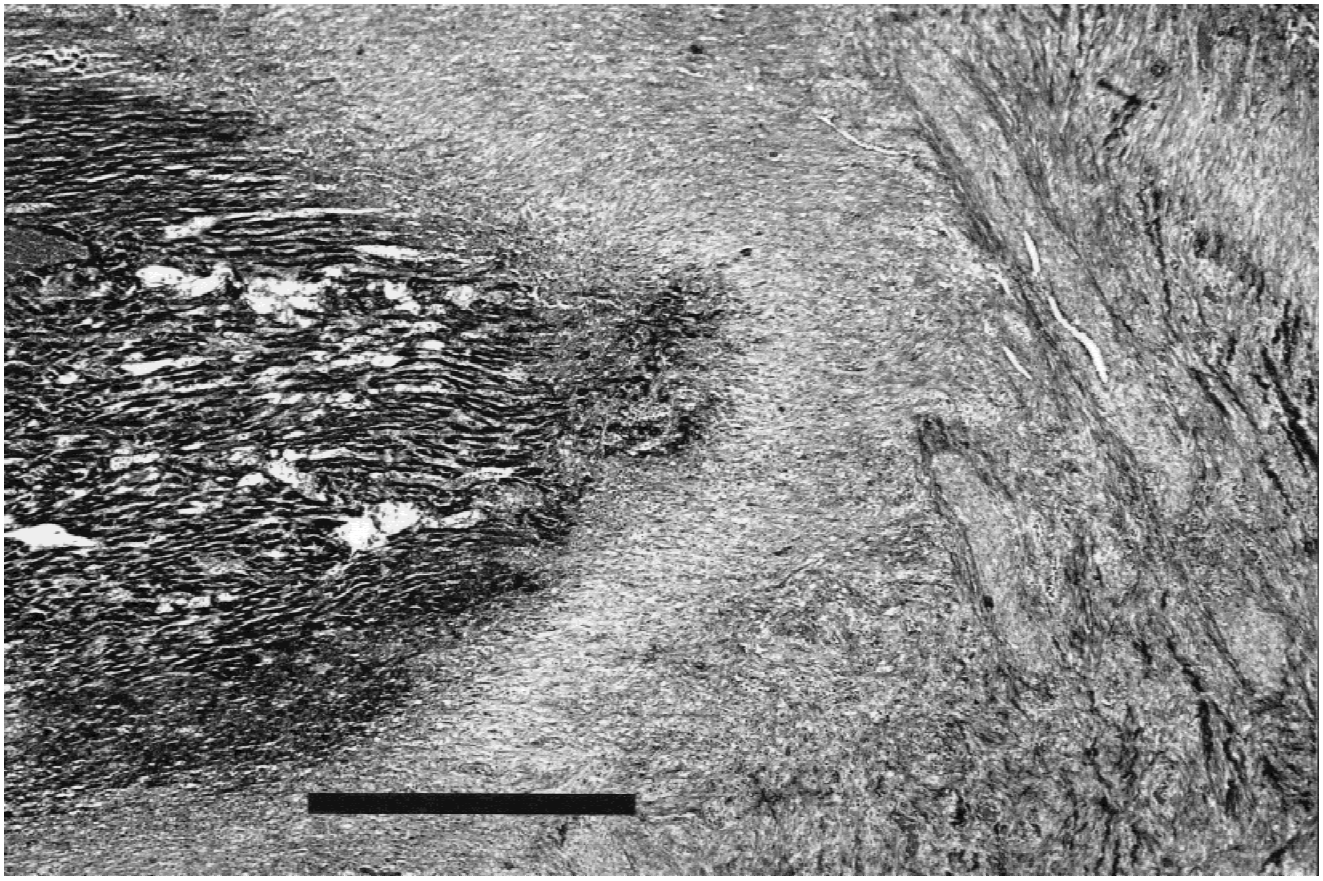

Fig. 4. Border of a channel area within an infarct at day 7. The central zone is filled with thermal necrosis debris and clots. Beyond it, is the granulation area of the channel and then that of the infarct. (Trichrome Masson stain; scale = 1 mm).

TABLE 1. Evolution of the Sizes of the Laser Lesions

Channel area	Day 0	Day 7	Day 14	Day 21	Day 28	Day 35
Lesion cross-section (mm^2)	8.5 ± 1.2	8 ± 1.3	4.3 ± 1.2	3.5 ± 1.9	2.4 ± 0.7	2.1 ± 0.1
Necrotic area (%)	—	37 ± 2	19 ± 10	10 ± 1	0 ± 0	0 ± 0
Granulation/scar area (%)	—	63 ± 2	81 ± 10	90 ± 1	100 ± 0	100 ± 0

the direction of the myofibrils (i.e., across the fibers).

Numerous reports have studied the physiological effects of TMLR on acute ischemia. It is worth emphasizing to note that studies claiming a positive effect of TMLR in dogs did not measure blood flow [9,10], whereas those that found no positive effect did measure collateral flow [11–16], which is a crucial determinant of infarct size in canine studies. Moreover, in our study the infarctions in the TMLR-MI group were transmural, underlining the absence of protection provided by channels in this model.

Most autopsy studies analyzing histological characteristics of the channels in chronically ischemic myocardium confirms the progressive occlusion of channels by scar tissue, with a similar time course [17–20]. However, two isolated reports [21,22] claim evidence of channel patency. The same remark as in the experimental setting concerning the small size of these so called patent channels is valid here. None of these studies mentioned the macroscopical findings of the endocardial surface.

Long-term improvement of the left ventricular function has never been clearly demonstrated, mainly because of the poor reproducibility of the results in estimating left ventricular function. Ejection fraction, which is the most commonly used method, is highly dependent on loading conditions. However, regional motion analysis improved at three months in two studies, one experi-

mental [8] and one clinical [32] using ultrasonic crystals and dobutamine stress test respectively. As there is no objective evidence for long-term channel patency, a frequently mentioned potential mechanism is the neovascularization induced by laser lesions. Although Kohmoto et al. [23] and Yamamoto et al. [33] recently found increased vascular growth in the immediate vicinity of the channels in a dog model, the capacity of these vessels to provide nutritive blood flow remains to be determined.

One aspect of the healing process may deserve further attention, namely the reduction of the channel area resulting from the scarring process. In our study the cross-sectional area of the laser lesion measured initially 8.5 ± 1.2 mm^2. The scar area at five weeks measured 2.1 ± 0.1 mm^2, representing a 75.3% reduction of the initial area. In the study by Fischer et al. [6] area measurements were within the same range with a 59% reduction at 2–3 weeks and a 93% reduction at six weeks. The slight difference in the area measurements might be related to our use of computed morphometrical analysis, which is likely to be more precise than the elliptical approximation [6]. However both studies show clearly a marked cicatricial contraction of the channel area by one month. Applying the Laplace law, this contraction effect could reduce the cavity diameter and therefore the wall stress and the oxygen consumption. If such a mechanism was involved, the type of laser could be relevant. Although no histological difference could be established between Ho:YAG and CO_2 laser, the size of the lesion with the Holmium:YAG laser is more than twice larger [6]. Therefore, its retraction effect is potentially more important. Further studies are needed to explore this mechanism as a potential explanation for the improved angina class and regional wall motion observed after TMLR.

The main limitation of this study lies in the fact that we compared the effects of TMLR performed on healthy vs. acutely ischemic myocardium, whereas clinically, TMLR has proven to improve angina in chronic ischemic disease. Whether our findings pertain to the clinically chronic setting remains to be determined.

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